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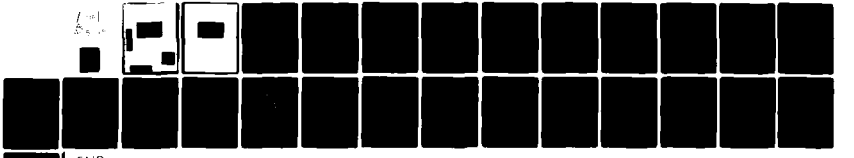

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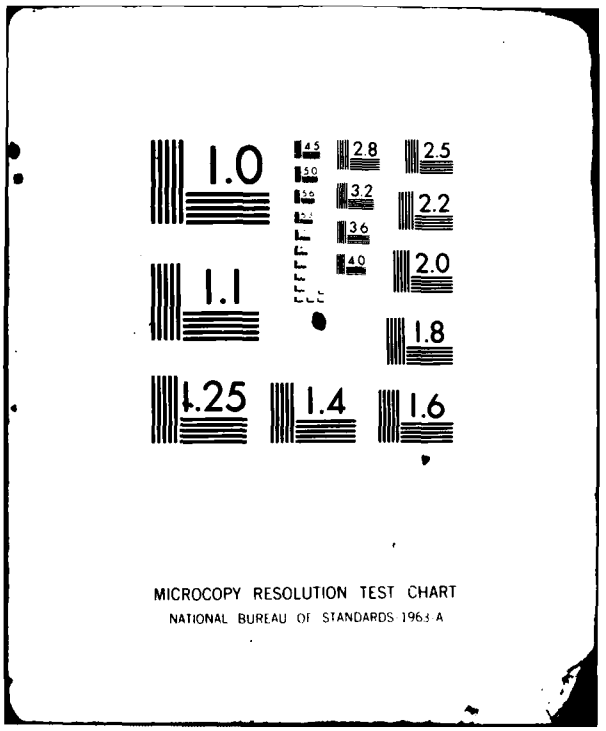
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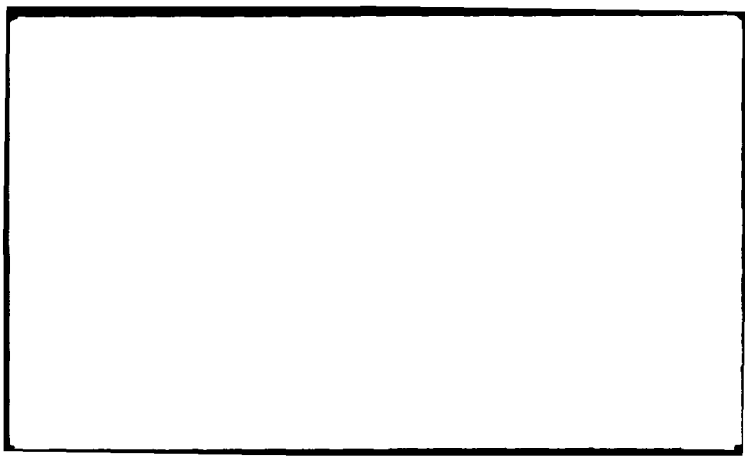

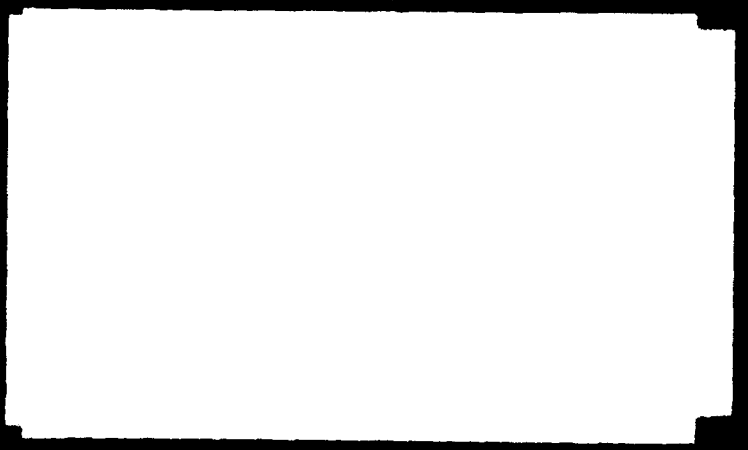

FINAL REPORT

DOSIMETRIC AND BEHAVIORAL ANALYSIS OF MICROWAVE-DRUG SYNERGISTIC EFFECTS ON OPERANT BEHAVIOR IN THE RAT

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to

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
BETHESDA, MARYLAND

Richard H. Lovely, David L. Lundstrom,
and Richard D. Phillips

December 18, 1981

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Five male Long-Evans rats, maintained at 80% of their free-feeding weight, were trained to bar-press for food reward on a one-minute fixed-interval (FI_1) schedule of reinforcement. Once stable FI_1 baseline response rates were established, dose-response functions were generated for Chlordiazepoxide HCl (CDZ). Subsequent treatments with CDZ were followed by 30 min. pulsed microwave radiation (MWR) and FI_1 behavioral assessment. Pulsed MWR exposures were in the far zone of an anechoic chamber at an averaged incident power density of 1 mW/cm^2 (PRF = 300/sec, 3 μsec pulse width). After 2 replications of the combined

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treatments another CDZ dose-response function was generated. This was followed by 3 more CDZ and MWR replications the first of which was carried out at an averaged incident power density of 1 mW/cm^2. Increased rates of response for the CDZ and 1 mW/cm^2 MWR treatment were demonstrated relative to initial CDZ dose-response functions in 4 of 5 rats tested. However, the dose-response functions for CDZ alone, that were generated following this apparent synergy showed the same shift in response rate. Furthur, the 8 mW/cm^2 pulsed MWR combined with CDZ also produced data similar to the 1 mW/cm^2 post-MWR exposure CDZ dose-response functions for the animals tested. Thus, we were unable to replicate an earlier demonstration of synergy between CDZ and MWR. The most likely explanation for the differences in our data from that of other investigators would seem to be our far zone exposure protocol as opposed to an earlier study that exposed rats in the near zone, viz., MWR dosimetry.

INTRODUCTION

Research examining the biological effects of exposure to microwave energy has made it clear that functions of the central nervous system including behavior are sensitive to impinging electromagnetic fields (e.g., see Tyler, 1975; Adey, 1980; Justesen, 1980). Most studies that have resolved effects on behavior at low levels (less than 10 mW/cm^2) of incident energy have examined schedule (of reinforcement) controlled behaviors where deviations from stable behavioral baselines occur as a consequence of microwave exposure (Thomas, Finch, Fulk and Burch, 1975).

Quite recently schedule controlled behavioral baselines that are a product of certain psychoactive drugs have been shown to be particularly sensitive to change if examined after exposure to pulsed microwaves. For example, Thomas and Maitland (1979) found that a 30-minute exposure to 1 mW/cm^2 pulsed microwaves following injection of varying doses of d-amphetamine produced a reduction in the drug dose necessary to change DRL behavioral baselines. The generality of a drug-microwave synergy was then extended to the commonly prescribed tranquilizer chlordiazepoxide (Thomas, Burch and Yeandle, 1979). In the latter study, drug dose-dependent increases in response rate on a fixed interval 1-minute schedule of reinforcement were demonstrated in four rats. If a 30-minute exposure to pulsed microwaves followed the drug injection, then greatly potentiated drug effects on the fixed interval behavioral baseline were observed when behavioral testing began immediately following the combined drug-microwave treatment.

While the two studies by Thomas and his colleagues found effects at averaged power densities of 1 mW/cm^2, it is difficult to translate the densitometric value to a meaningful dose rate because the exposures were carried out

in the near field of his 2450 MHz source. In an attempt to better characterize the dose rate and distribution associated with particular power densities, we attempted to replicate the study reported by Thomas, Burch and Yeandle (1979) by dosing rats with microwaves and chloridazepoxide (singly and in combination) in the far zone of a previously, well-defined, plane wave field (Phillips, Hunt and King, 1975). With the exception of near-field exposures versus far-field exposures, we attempted to literally replicate the study of Thomas, Burch and Yeandle. Other minor differences and similarities between Thomas et al., and our attempt to replicate their work are summarized in Table 1. Our traning and treatment procedures are described in the following paragraphs.

TABLE 1. Comparison of Microwave Exposure Parameters Employed by Thomas et al. (1979) and those Employed in Battelle Studies

Frequency (GHz)	Pulse Width	PRF	Temp. (°C)	Ave. PD	Other Parameters
* 2.45	2 μsec	500	23 ± 2	1 mW/cm^2	Near field, electric field vertically polarized, rat positioned with long axis of its body perpendicular to the K-vector.
** 2.88	3.0 μsec	300	23.5 ± 1.5	1 mW/cm^2	Far field, rat parallel to E-vector and perpendicular to the K-vector.

*Parameters employed by Thomas et al.
**Parameters employed by Battelle

METHODS

Subjects

In attempting to replicate the Thomas study, extenisve efforts were made to maintain all biological parameters identical to those originally reported. These parameters were: source, strain, age, sex and body mass of the experimental animals. Sixteen male, SPF, Long-Evans hooded rats were obtained from Charles Rivers (Portage, MI), eight of which were randomly selected for the study. When their free-feeding weights reached 325 to 375 grams, they were reduced to 80% of their free-feeding mass by restricting daily access to food; water was available at all times. Each animal was individually housed in hanging metal cages with wire-mesh floors. Overhead florescent lighting was maintained on a 12-hr on, 12-hr off cycle (lights were turned on at 0700).

Apparatus

Daily testing was carried out in a standard operant chamber for rodents (Lehigh Valley). The operant test chamber was maintained in a walk-in, sound-attenuated chamber. A television camera provided remote monitoring of performance on a video screen. Management of animal's performance, reinforcement schedules and reinforcement delivery (45 mg. Noyes food pellets) was accomplished by solid state programing modules located outside the sound-attenuated chamber. Pulsed microwaves were generated by an APS/20E radar transmitter. Radar pulses, incident on the animal, emanated from a 16-dB, standard-gain horn. The animal was located approximately 10 ft from the horn aperture, placing the rodent in the far field. Both analog and digital power meters monitored forward power in the waveguide. Far field densitometry was measured with a Narda Meter (Model 8321). Temperature in the anechoic and operant chambers was monitored with alcohol thermometers.

Densitometery and Dosimetry

Forward power in the waveguide was adjusted to produce unperturbed densitometric readings of 1 mW/cm^2 averaged incident power density at the location of the rat and its Bollman holder. Prior work carried out in this facility (Phillips, Hunt and King, 1975), employing twin-well calorimetry, determined that the specific absorption rate (SAR) in a rat positioned parallel to the electric field was approximately 200 $\mu W/gm$ for each 1 mW/cm^2 incident on the animal when located in the far field.

Procedure

After the eight rats selected for the study had stabilized at 80% of their free-feeding body mass, they were shaped (via successive approximations) to lever-press for Noyes food pellets on a schedule of continuous reinforcement (fixed ratio 1:1). Once this task was learned, they were shaped to lever-press on a 1-minute, fixed-interval (FI_1) reinforcement schedule. After 2 to 3 months of training, a stable baseline rate of response was established for each rat. The intitial group of eight rats was then culled to five, eliminating three rats which responded most erratically.

Next, the animals were adapted to restraint in Bollman holders in the microwave anechoic chamber for 30 mintues/day prior to the 1-hour FI_1 session. Several weeks were required for the baseline rates to stabilize. At this point, we assessed the effects of three 30-mintue, microwave-radiation-only, exposures (2.88 GHz, 3 μsec pulse width, 300 pulses/sec) at an average power density of 1 mW/cm^2, and three saline-only (1 ml/kg) treatments on FI_1 responding. The rates of response for each rat were not altered from their baselines under either of these conditions.

Subsequent to these assessments, a dose-response function was generated for chloridazepoxide hydrochloride (CDZ) alone at 1.0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg/kg. Three replications were obtained for each animal. The CDZ was administered intraperitoneally on Tuesday and Thursday of each week; baseline assessments without drug treatment (restraint only) were determined on Mondays and Wednesdays. A saline only treatment was carried out on Fridays. Because of the variance at each dose across the three replications of the dose-response function, we elected to generate a fourth dose-response function. Unfortunately, the fourth function was not less variable than the first three (for the group as well as for individuals).

We then proceeded with the second (synergy) phase of the study, despite the fact that the dose-response functions were both less pronounced and more variable than those reported by Thomas et al. During the synergy phase, no-drug baselines were obtained every Monday and Wednesday; CDZ and microwaves combined, were assessed on Tuesdays and Thursdays except that the dose-dependent effects of CDZ alone were assessed every other Thursday. On Fridays, we assessed saline-alone, microwaves-alone, or saline and microwaves combined; rotating these conditions throughout the course of the study. The first and second replications of the synergy phase suggested, at most, a weak synergy for some rats. Subsequently, however, a fifth through eighth dose-response function was generated (after the microwave drug synergy phase). These functions demonstrated less variability and the drug-induced, dose-dependent response rates were slightly higher, typical of those reported in the Thomas study. A final synergy assessment was then carried out at 1 mW/cm^2. As with the earlier synergy tests, no clear-cut potentiation of the effect of CDZ on FI_1 response was observed.

The magnitude of the CDZ-potentiated behavioral baselines in replications five through eight made it clear that our earlier data from the synergy phase did not demonstrate an interaction between CDZ and pulsed microwaves. For this reason, we tested three of the rats (7, 10 and 15) following injection of CDZ and a 30-minute exposure to pulsed microwaves, averaging 8 mW/cm^2 incident power density. The rats were run at all CDZ doses for two replications employing the same paradigm as that used for the 1 mW/cm^2 synergy assessments.

RESULTS

Our findings are shown in Figures 1 through 5 (a separate figure for each rat). The ordinate values are responses/second. The abscissas (from left to right) are as follows:

- B = mean pretreatment baseline on FI_1 schedule
- $\mu\lambda$ = mean of microwave exposure only (before drug treatment)
- NDB (DRF) = mean no-drug baseline during dose-response replications
- NDB (Syn) = mean no-drug baseline during CDZ-plus-microwave dose-response replications
- S = mean saline only
- S + $\mu\lambda$ = mean saline-plus-microwave.

The abscissa numbers represent the dose (mg/kg) of CDZ given during replications one through four (●), replications five through eight (▲), and the three synergy replications at 1 mW/cm^2 (0). In addition, we also ran two synergy replications at 8 mW/cm^2 (Δ) (rats 7, 10 and 15). The bars are not error bars, but show the full dynamic range of response for dose-response replications one through four and five through eight. For each of the five rats, four <u>important</u> functions are plotted:

- CDZ dose-response function (replications one through four)
- CDZ dose-response function (replications five through eight)
- CDZ-plus-microwave function (0), representing the mean of three replications (for 1 mW/cm^2) or two replications at 8 mW/cm^2 (Δ).

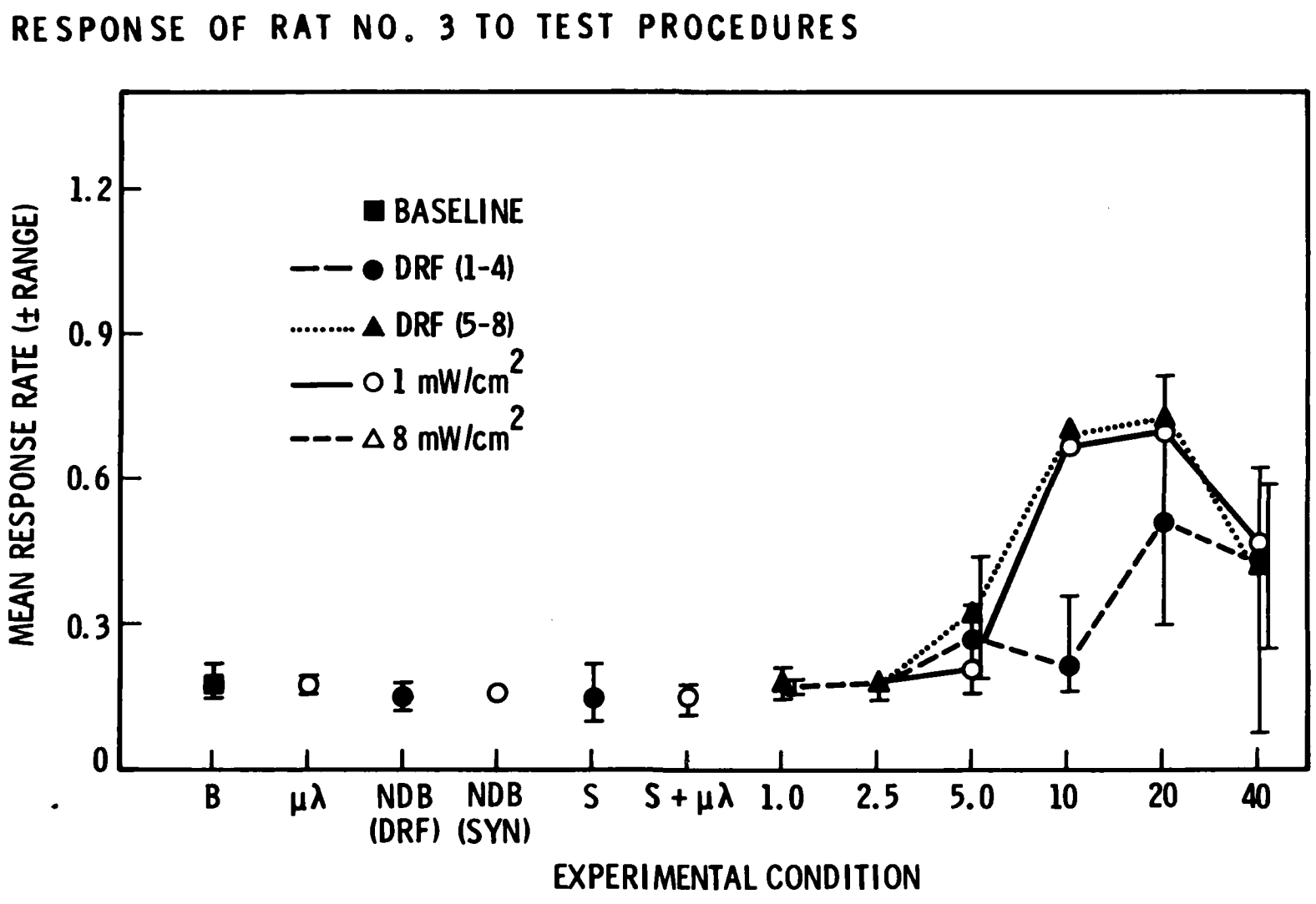

FIGURE 1. Mean number of responses per second for the various treatment conditions administered to rat #3.

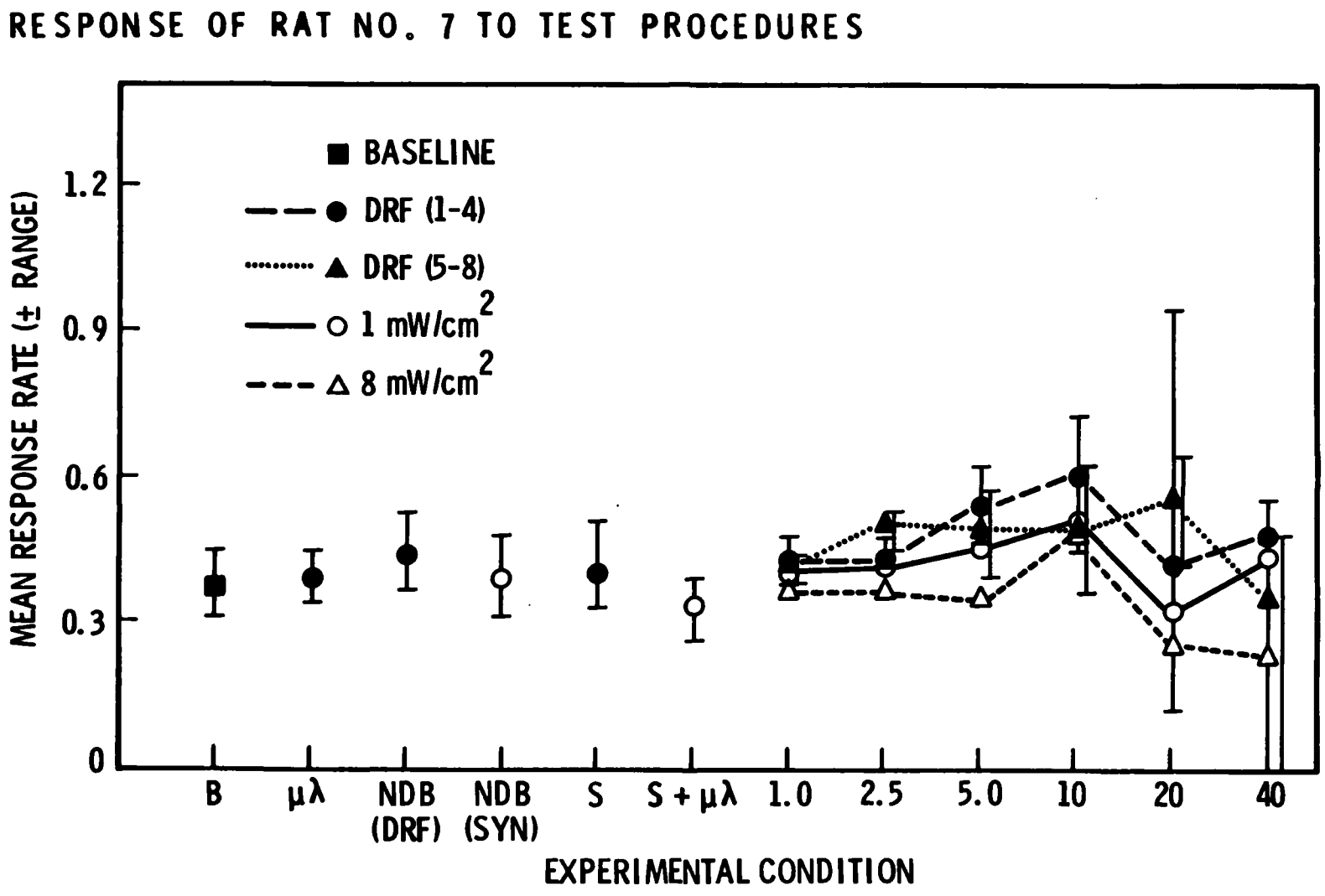

FIGURE 2. Mean number of responses per second for the various treatment conditions administered to rat #7.

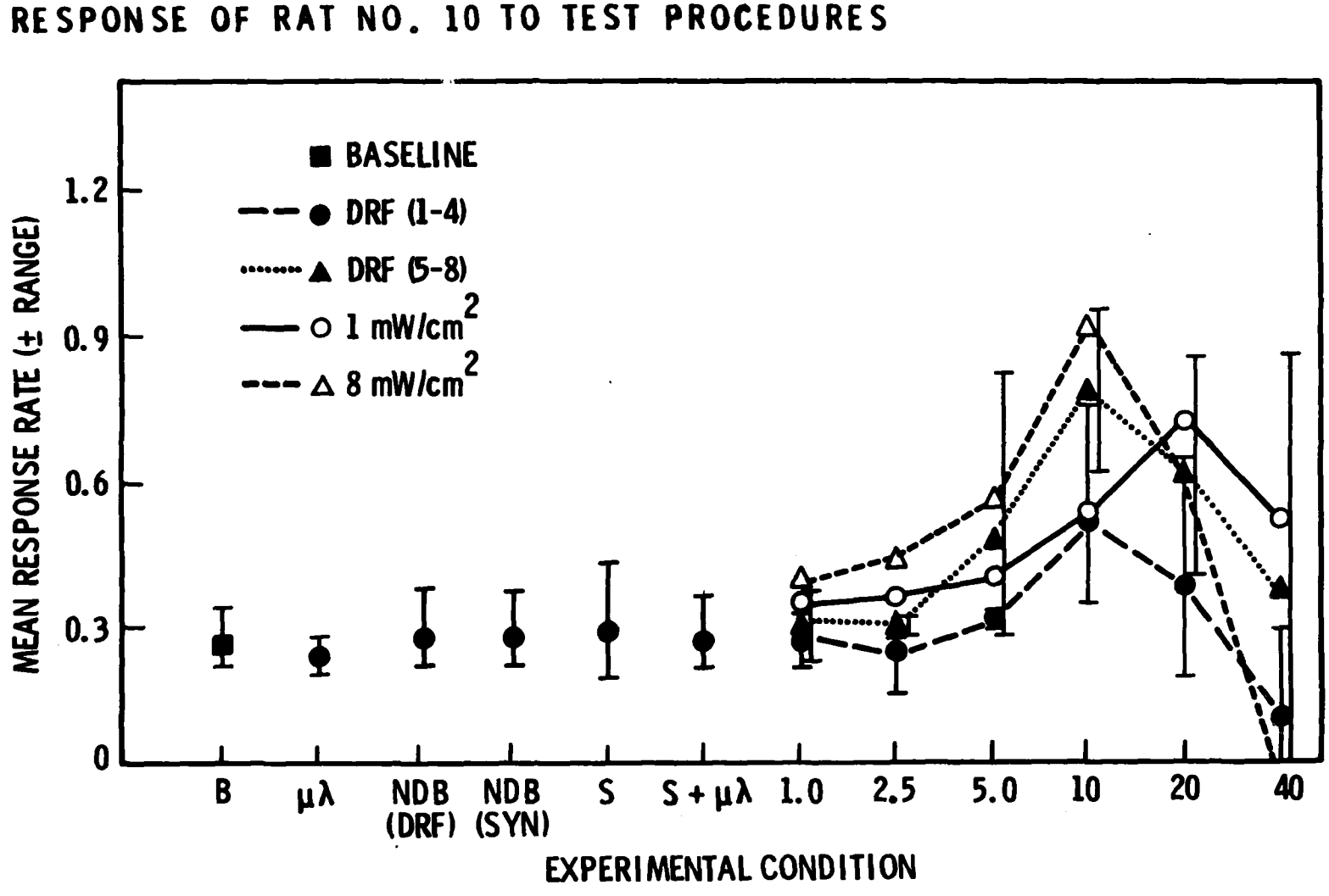

FIGURE 3. Mean number of responses per second for the various treatment conditions administered to rat #10.

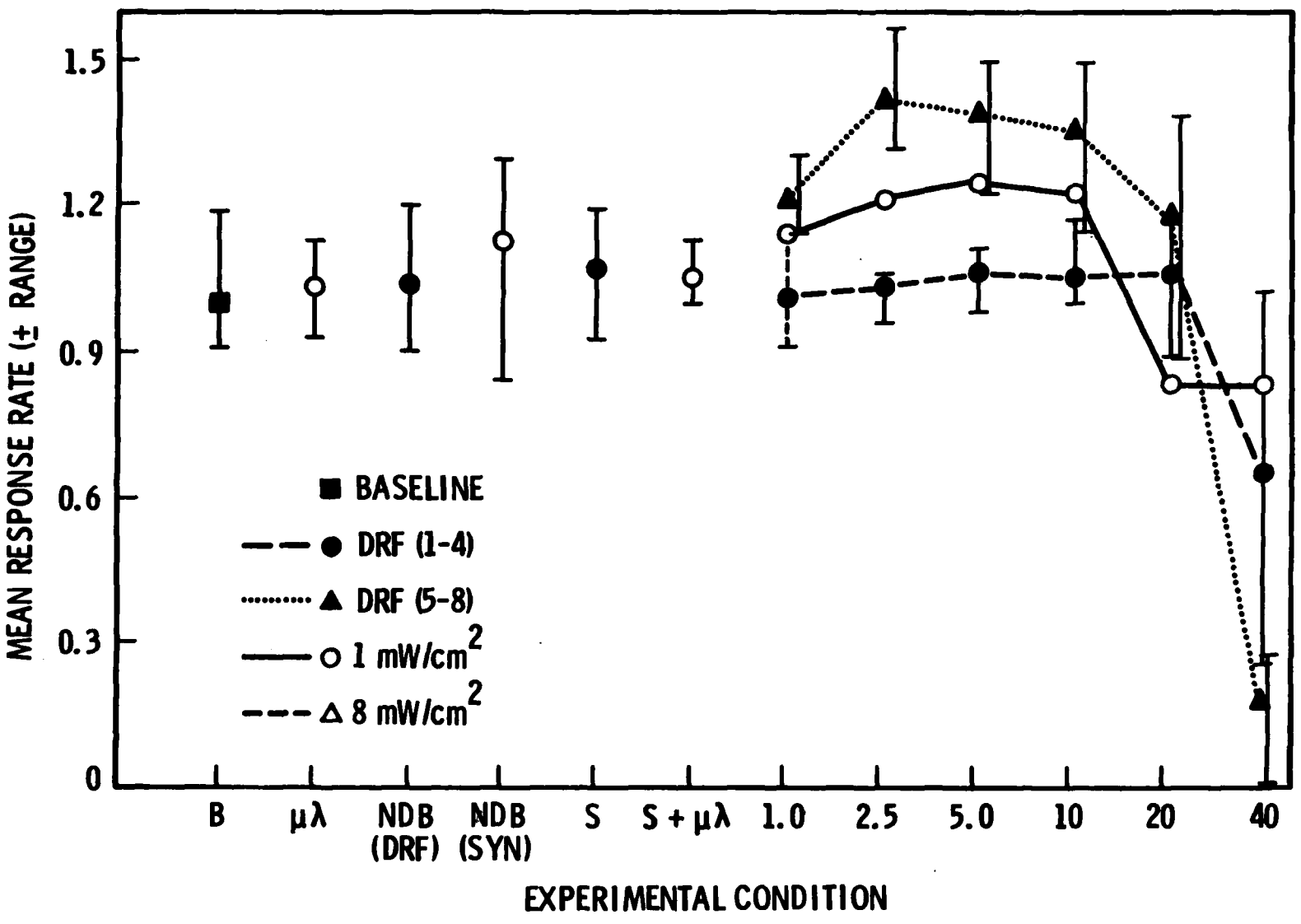

FIGURE 4. Mean number of responses per second for the various treatment conditions administered to rat #11.

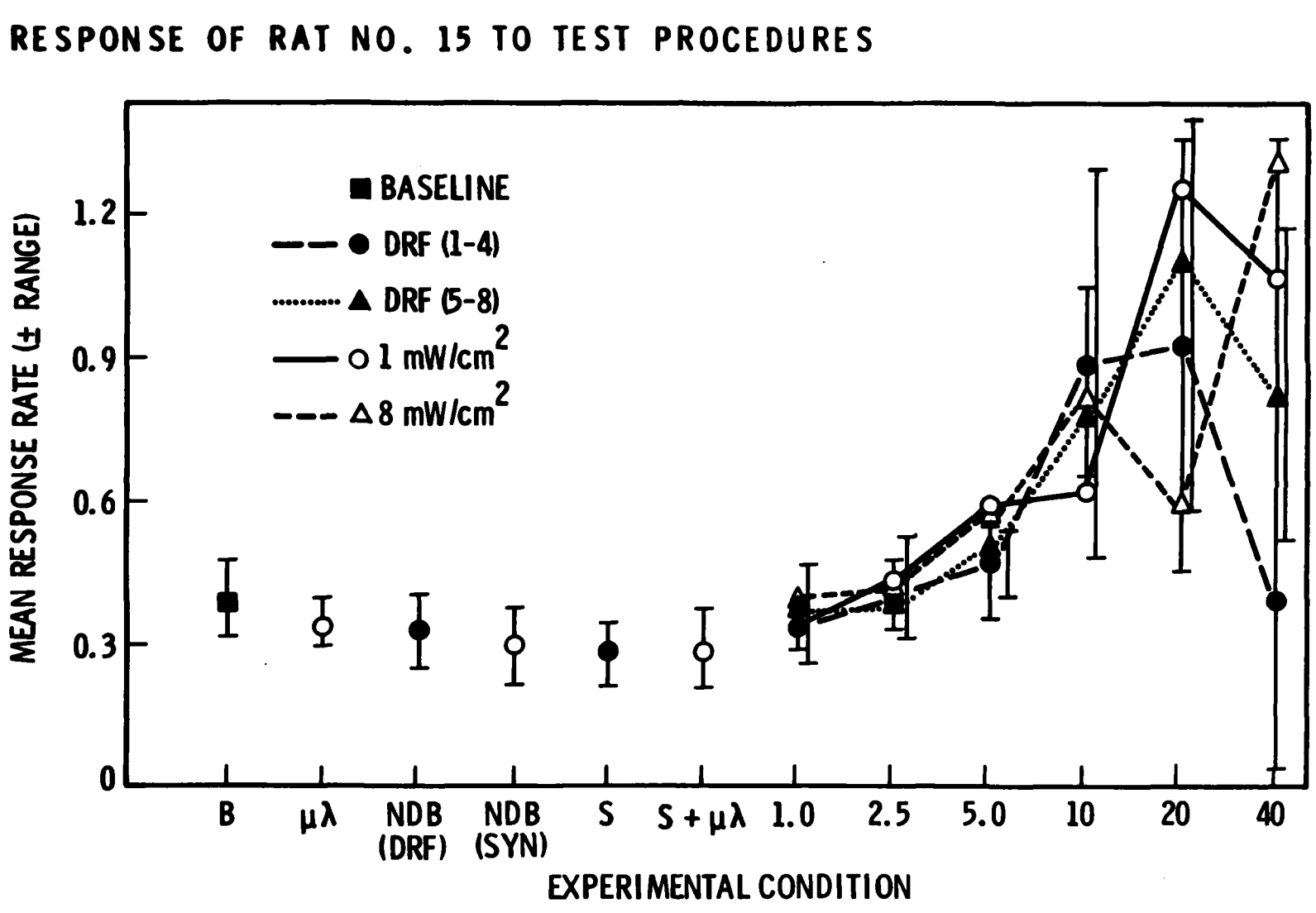

FIGURE 5. Mean number of responses per second for the various treatment conditions administered to rat #15.

DISCUSSION

The results of this experiment are fairly clear cut. In general, we were unable to demonstrate a synergistic effect of 2.88 GHz pulsed-microwave radiation with CDZ when microwave exposure is performed in the far field at averaged incident power densities of 1 mW/cm^2 or 8 mW/cm^2. These values correspond to an SAR of 0.2 mW/gm and 1.6 mW/gm, respectively. One possible exception to the foregoing generalization can be seen in Figure 3. The response rate of rat #10 to CDZ, when tested after exposure to 8 mW/cm^2 pulsed microwaves, appears to be somewhat potentiated. But the magnitude of the potentiation, relative to the drug-alone response rates obtained in replications five through eight, is not very impressive when considered in light of the findings of Thomas et al. (1979). Further, the suggestion of a weak effect is seen in only one of the three rats tested at 8 mW/cm^2. Finally, it is just as possible that the weak effect is a result of repeated injections and testing, or of age; a conclusion supported by the chronological increase in response rate of rat #10 over four major phases of treatment involving drug administration.

The multiple drug-dose-dependent changes seen in rat #10 were typical of other rats in this study. Rat #3 and #11 showed similar time-dependent changes in responses to varying doses of CDZ. We have no explanation for these changes. It could by argued that the animals in question may have developed a hypersensitivity to CDZ. However, this is unlikely because hypersensitivity typically occurs only after development of a drug tolerance, followed by removal from the drug for a substantial period of time. Following drug tolerance and drug withdrawal, an animal will often show an exaggerated response (i.e., hypersensitivity) to the administration of a particular drug dose. In terms of the procedures employed here, it is difficult to reach the conclusion that these

data are the manifestation of CDZ hypersensitivity, albeit they appear to reflect this. Nor is age, per se, the basis of the observed changes in dose-response functions. In a pilot study, we used older (untreated) rats from the same animal shipment to examine the effects of CDZ on ad libitum drinking for 1 hour immediately following injection, using the same range of doses as those in the main study. Even in these naive rats of similar ages, we found that at about the time a third dose-response function was generated, several rats drank water as if they had developed a hypersensitivity to CDZ. With this in mind, in addition to the findings of Thomas et al., who trained rats for more than a year, we are inclined to dismiss age as a factor which might account for the time-dependent changes in our dose-response functions.

In addition to the three rats discussed above, two other response patterns were observed. As shown in Figure 2, rat #7 failed to respond dramatically to varying doses of CDZ. By contrast, rat #15 generated a crisp dose-response function from the beginning of the study much like the rats of Thomas et al, but that is the end of the similarity since rat #15 (like the other rats in this study) failed to show a potentiated response rate after CDZ and microwave pairings.

The variability of our data not withstanding, we are forced to conclude that 2.88 GHz pulsed microwaves at average power densities of 1 mW/cm^2 and 8 mW/cm^2 do not act to potentiate the effects of CDZ on rats' FI_1 rate of response. While extensive care was taken to maintain constant variables, with regard to the study by Thomas et al., one major parameter <u>was</u> altered; i.e., exposure in the far zone in our study, as opposed to the near zone exposure by Thomas et al. We are inclined to suspect that the differences between energy capture by the rat calvarium in near zone versus far zone exposures (i.e., the length of the rat skull is very close to resonance at 2450 MHz), most likely accounts for the differences between the two studies.

Experiment II

The schedule-controlled behavioral-baseline approach (while sensitive) was very time consuming. It took 1 year and 4 months to demonstrate, in five rats, that no far-field synergy effects occured at incident energy levels of 1 or 8 mW/cm^2. For this reason, we attempted to find a behavioral assay which would be sensitive to the effects of CDZ, but which would also be less time consuming. We chose to examine the dipsogenic effects of CDZ on the water-deprived rat. Rats which are allowed to drink water for only a few minutes per day, consume more water following an injection of CDZ than they would drink otherwise (Riley and Lovely, 1978).

Our first nonoperant study was a small-scale 2 x 3 factorial design (6 cells with N = 4/cell); N = 24. The factorial design was an attempt to determine the best parameters for CDZ-induced drinking in rats. Ninety-day-old, naive SPF, Long Evens rats were obtained from Charles Rivers (Portage, MI). Rats were allowed access to water for either 10 or 15 minutes/day (Factor 1, N = 12 per level). After stable baselines were established, the rats were injected with saline prior to drinking sessions, over 2 consecutive days, to adapt them to being held and given injections. On the following day, the rats were weighed and, 30 minutes prior to the drinking sessions of 10 or 15 minutes, were injected with 2.5-, 5.0-, or 10 mg/kg of CDZ (Factor 2, N = 8 for each of three doses of CDZ).

Although we did not see the magnitude of dipsogenesis we had hoped for, there were some interesting, statistically reliable effects (Table 2). Across all drug doses, an interval of 15 minutes allowed more time for greater fluid consumption. This is, of course, what would be expected; however, the rats in the 15-minute sessions had lower baselines than the 10-minute drinkers throughout training. The most marked effect was at at the 5.0-mg/kg dose level, al-

TABLE 2. Mean cc Water Consumed (±SEM), Following Placebo or CDZ Injection, as a Function of Dose and Time Allowed to Drink

CDZ Dose (mg)	Ten-Minute Test		Fifteen-Minute Test	
	Saline	CDZ	Saline	CDZ
2.5	17.7 ± 2.1	16.6 ± 0.7	15.9 ± 0.9	17.8 ± 0.6
5.0	16.1 ± 0.4	17.3 ± 2.6	15.4 ± 0.9	18.4 ± 1.3
10.0	16.4 ± 1.3	14.3 ± 1.7	16.3 ± 0.5	16.0 ± 3.5

though the 2.5-mg/kg level also produced marked effects and less variance. Based on this pilot study, a drinking period of 18 minutes and a CDZ dose of 2.5 mg/kg were selected for the main study. This drinking period and drug dose were chosen because we needed a basic drug effect (such as that seen at 2.5 mg/kg) which was less than that which induces maximal drinking (such as that seen at 5.0 mg/kg), so that possible microwave potentiation of the drug effect would be observable; i.e., one does not want a "ceiling" effect in the non-microwave-exposed, drugged, control rats.

Because of the results of the rangefinding study described above, the following protocol was selected for our final study. Four groups of six rats each were acclimated to handling and restraint, and placed on an 18-minute/day watering schedule. The rats were from the same population as those used in the pilot study and averaged 105 days of age. The rats were weighed daily, then placed in Bollman holders which, in turn, were placed in the anechoic chamber for 20 minutes after a 10-minute delay (to test drinking 30 minutes following restraint and injection), and were then tested for water consumption. The total microwave exposure time was shortened to 20 minutes so the 24 rats in the study could be singly exposed within an 8-hour period.

After about a week to 10 days of training (i.e., when water intake levels were stable within and across groups), each subset of rats received one of four

treatment conditions: Group 1 (injection control) was injected with saline and sham exposed to microwaves in the anechoic chamber (the APS/20E radar unit was maintained in the standby mode) for 20 minutes following the 10-minute delay. Group 2 (drug effect) was injected with 2.5 mg/kg CDZ and, after a 10-minute delay, sham exposed for 20 minutes in the anechoic chamber. Group 3 (synergy effect) was injected as Group 2, but exposed in the far zone to 1 mW/cm^2 (same pulsing parameters as in our operant study). Group 4 (microwaves-only control) was not injected, but was weighed, restrained, held for 10 minutes, then exposed for 20 minutes to microwaves only. As soon as a rat was removed from restraint and returned to the home cage, it was allowed 18 minutes access to water.

These four groups were tested on four separate occasions following treatment. During the latter part of the first drinking assessment (2.5 mg/kg CDZ plus 1 mW/cm^2 pulsed microwaves), a failure in the building cooling system allowed the temperature to reach 26°C in the microwave anechoic chamber. For this reason, the rats were given two recovery days (restraint only, followed by access to water for 18 minutes). The four treatment groups then underwent a second treatment identical to the first; i.e., saline plus sham exposure, CDZ plus sham exposure, CDZ plus pulsed microwaves, or microwaves alone. A third assessment differed only in the dose of CDZ given (5 mg/kg), while the fourth assessment employed a CDZ dose of 5 mg/kg plus pulsed microwaves averaging 8.0 mW/cm^2 in the far field of the anechoic chamber. The test sessions were separated from each other by two recovery days consisting of the 30-minute restraint, followed by 18 minutes access to water in the home cage. A summary of treatment conditions, as well as the mean outcome for each group, is presented in Table 3.

TABLE 3. Mean cc Water Consumed (±SEM) for the Four Groups Tested at Two CDZ Doses and Two Microwave Field Strengths. The top number of each pair is the mean of the prior two days (baseline). The lower number is the outcome of treatment.

	Saline plus Sham Exposure	CDZ plus Sham Exposure	CDZ plus Microwaves	Microwaves Alone
2.5 mg/kg CDZ and 1 mW/cm^2 pulsed microwaves (ambient temp. 26°C)	16.37 ± 0.82 15.67 ± 0.86	14.80 ± 0.25 15.25 ± 0.60	15.55 ± 0.36 16.67 ± 0.88	15.10 ± 0.32 16.25 ± 0.67
2.5 mg/kg CDZ and 1 mW/cm^2 pulsed microwaves (ambient temp. 23°C)	15.18 ± 0.71 16.75 ± 1.09	15.12 ± 0.54 16.33 ± 1.03	15.22 ± 0.46 15.58 ± 0.55	15.00 ± 0.88 15.67 ± 0.54
5 mg/kg CDZ and 1 mW/cm^2 pulsed microwaves (ambient temp. 23°C)	17.7 ± 1.19 16.5 ± 0.82	13.60 ± 0.88 15.50 ± 1.15	15.07 ± 1.03 15.75 ± 0.86	15.07 ± 0.81 14.33 ± 0.64
5 mg/kg CDZ and 8 mW/cm^2 pulsed microwaves (ambient temp. 23°C)	16.92 ± 0.51 15.33 ± 1.01	16.25 ± 0.83 16.01 ± 0.60	15.25 ± 0.75 16.83 ± 0.87	16.42 ± 1.23 15.25 ± 1.04
Cumulative difference from baseline (in cc)	- 0.4	+21.3	+25.1	- 0.5

Results and Discussion

The data in Table 3 are self-explanatory. The top number of every pair of means is the mean baseline water consumption prior to the specified treatment. The lower number is the mean water consumption produced by the specified treatment. Relative to the standard errors obtained, there are no significant effects of treatment with CDZ, pulsed microwaves alone, or microwaves plus CDZ. However, there is more to the story than this simple conclusion. We suspect that the small sample size was an important factor (we could only

place three rats in the anechoic chamber per hour). Had we exposed or sham-exposed four rats at a time, we could have greatly increased the group sample size and in turn might have resolved the differences between groups due to the drug or drug plus microwave treatments. We argue for this conclusion for two reasons. 1) The CDZ plus sham-exposure group and the CDZ plus microwave group showed higher mean water consumption scores over their pretreatment baseline in all cases except one (i.e., seven of eight outcomes), while the control groups showed only chance increases (three of eight outcomes). Statistical analyses (t-tests), however, failed to reveal significant differences which we attribute to the small magnitude of effect relative to the error variance. 2) Larger sample sizes might have resolved the hypothesized effects based on the cumulative difference scores shown at the bottom of Table 3. These values are the difference scores in water consumption relative to the mean baseline summed over all animals in all tests. If the null hypothesis is true, one expects this mean difference score to be "0". As can be seen in the saline plus sham-exposure and microwave-alone control groups, the summated difference scores from baseline are a good fit for the null hypothesis (no effect). But, look at the cumulative difference scores for the two groups receiving CDZ. There appears to be a clear cut increase in water consumption due to the administration of the drug CDZ (pooled over all four tests) and an even greater increase in water consumption due to the combined administration of CDZ and microwaves. Unfortunately, these cumulative differences are taken over different experimental treatments and are based on repeated measures in the same subjects. As such, they are not amenable to statistical analysis. Nevertheless, they are very suggestive and are outcomes that would be predicted by the CDZ-microwave synergy hypothesis argued for by the original findings of Thomas et al. (1979).

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